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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,181	03/30/2001	Jingyue Ju	0575/62948/JPW/ADM/BJA	9161

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John P. White, Esq.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,181	JU ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06 June 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 May 2005 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 74-92 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of

> ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

4. Acknowledgement is made of applicant having directed attention to page 32, lines 7-23; and page 48, lines 26-29, of the originally filed specification as providing support for the amendment to claim 74, the sole independent claim. Upon review of the cited passages, support for a generic claim comprising these newly added limitations cannot be found. While page 48, lines 26-29, does provide support for passing fluid through a channel multiple times, such is in respect to using "a glass capillary" and that the channels are in a "chip." Clam 74 does not recite these other limitations and a review of the cited passages, including Fig. 12, does not support their broader application.

5. For purposes of examination, claim 74 has been interpreted as encompassing a method whereby the nucleotide sequence of virtually any DNA can be determined, including intact chromosomes, as well as any number of fragments of any length and of any degree of similarity to that of the DNA that the artisan truly wishes to sequence. The claimed method has also been construed as encompassing the performance of the claimed method under virtually any condition that would result in any primer extension product, including primer extension products derived from non-target DNA molecules. And the claimed method has been interpreted as encompassing the accurate, reproducible sequencing of any number of DNA sequences in a simultaneous format where the same labels are used for all primer extension products derived from all DNA templates.

6. The claimed method has also been construed as encompassing the use of a system whose surface has been "coated with a compound" where the coating is by covalent or non-covalent binding means.

7. The claimed method has also been construed as encompassing the simultaneous determination of the masses of an infinite number of DNA fragments, irrespective of the template(s) they were derived from, including a heterogeneous mixture comprising premature termination products, full length products of short templates, erroneous incorporation of nucleotides in full length sequences, etc.

8. Said claim has also been interpreted as encompassing the use of a system where a plurality of wells are in series for each channel, and that the sample is immobilized to the coated surface of the channels by a single passage of the sample through said channels and wells.

9. The claimed method has also been interpreted as encompassing the use of coated channels that are open/exposed on one side as well as channels that are entirely closed except for the ends.

10. The claimed method has been interpreted as encompassing the release of the immobilized DNA sequencing fragments by virtually any means, which include but are not limited to, heating, application of light, application of one or any combination of chemicals, including but not limited to alkaline degradation.

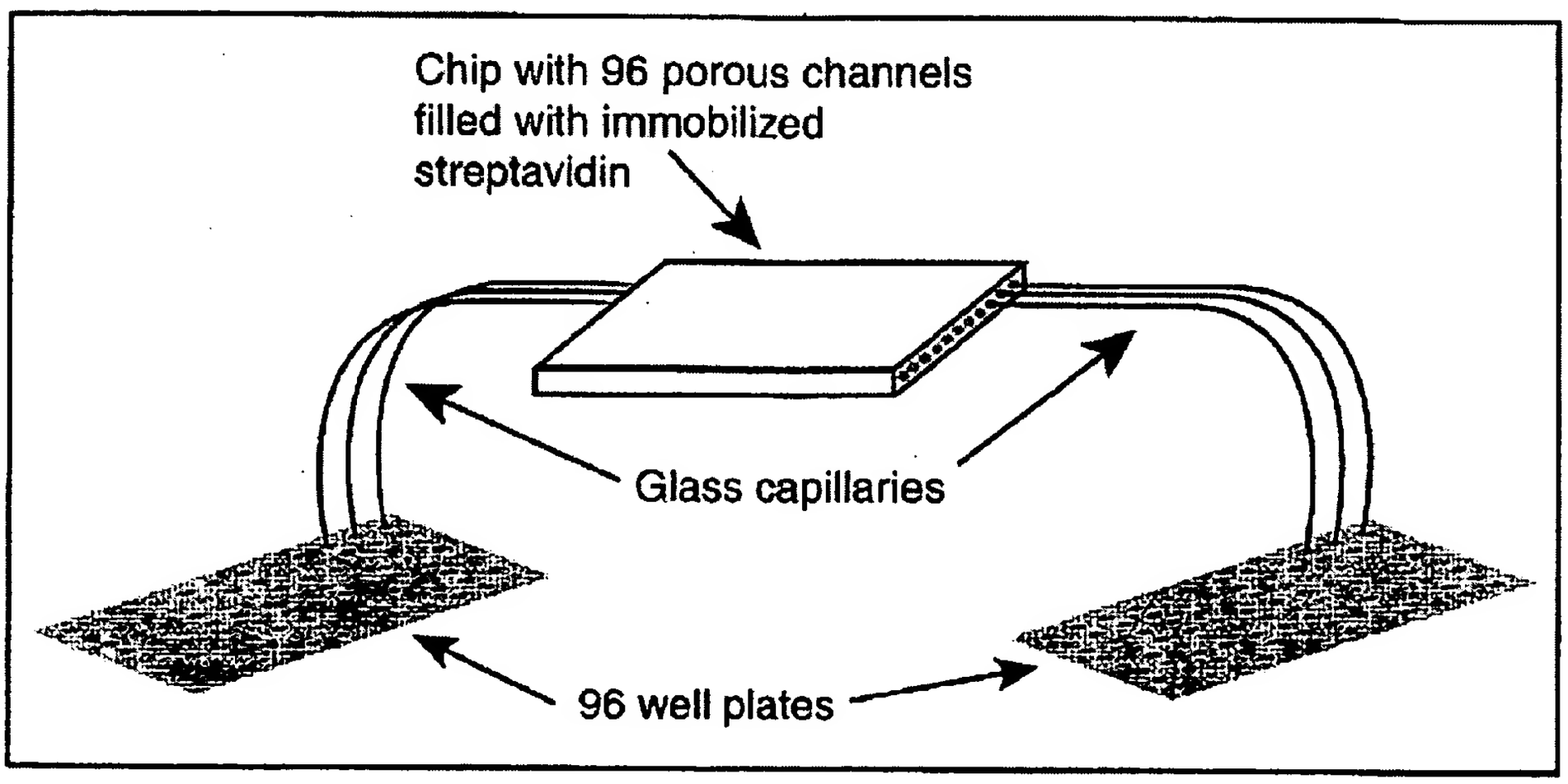
11. Said claim has been interpreted as encompassing determining the difference in molecular weight between different labeled DNA sequencing fragments via mass spectrometry, where the DNA sequencing fragments have not been further manipulated or modified since passage through the channel(s) and well(s). To that end, the claimed method fairly encompasses

practicing a method where the samples are not free from alkaline or alkaline-earth salts, or any other contaminant. The instant specification, however, cautions artisans thusly:

> However, in order to obtain accurate measure of the mass of the sequencing DNA fragments, the samples must be free from alkaline and alkaline-earth salts. Samples must be desalted and free from contaminants before the MS analysis.

A review of the specification, including the passages cited by applicant, fails to find an adequate written description of where mass spectrometry is performed on the DNA sequencing fragments where the sample contains any of the above-noted contaminants.

12. As noted above, the claimed method has been interpreted as comprising a plurality of wells connected via a channel, where the channel and wells are within a chip. A review of the disclosure, however, fails to find an adequate written description of such a device. Rather, the specification has been found to provide a description via Fig. 12, of two 96-well plates that are connected via glass capillary tubes to corresponding single channels in a chip.



It is noted with particularity that the device described lacks any means for applying pressure such that any one, much less 96 different samples could be passed through the coated channels in one direction, much less back-and-forth, thereby permitting/enabling the binding of the DNA sequencing fragments.

13. As noted above, the claimed method has been interpreted as requiring but a single pass of the sample through the channels, however, page 48, lines 26-29, describes a method requiring pressure to be applied in reverse in order to drive "the sample through the channel multiple times," thereby ensuring a high efficiency solid phase capture. Assuming *arguendo*, that the specification does suggest performing but a single pass of the sample through the channel, the specification has not been found to provide an adequate written description of how adequate quantities of DNA sequencing fragments are to be bound, and subsequently released and then analyzed such that the nucleotide sequence could be accurately and reproducibly determined, especially when the quantity of starting material is severely limited.

14. The claimed method has also been interpreted as encompassing the simultaneous sequencing of multiple DNA sequencing fragments in a common channel. To perform such a maneuver would present situations where multiple signals would be generated at the same time, yet would correspond to the different templates. The use of knowingly different DNA fragments will cause situations where the nucleotide sequence is anything but clearly resolvable. The specification has not been found to provide an adequate written description of how this issue is to be overcome.

15. The claimed method fairly encompasses the use of mass spectrometry in the analysis of the DNA fragments. The use of lasers in performing mass spectrometry is recognized in the art

as causing significant problems in sequencing. In support of this position attention is directed to

US Patent Application Publication 2002016842A1 teaches at paragraph 13:

> A problem encountered with MALDI of simplex DNA is breakage. Initial trials with short homogenous simplexes revealed severe fragmentation problems ("Matrix-assisted laser-desorption mass spectrometry of DNA using an infrared free-electron laser," Haugland, R. F. et al.; Proc. SPIE-Int. Soc. Opt. Eng., 1854 (FEL), 1993). Two distinct molecules of lower mass are split off by a break in the deoxyribose-phosphodiester backbone of single stranded DNA. Even for a homogenous population of single stranded DNAs, the resultant fragments have a broad range of lower masses. For projected heterogeneous single stranded Pop as inputs for sequencing, lower mass members will be within the fragmentation background and thus harder to recognize.

The specification of the subject application has not been found to provide an adequate written description as to how art-recognized issues are to be overcome.

16. In view of the breadth of the claims, the limited written description provided, the specification has not been found to provide an adequate written description of the invention. Similarly, the specification has not been found to reasonably suggest that applicant was in possession of the invention at the time of filing. Therefore, and in the absence of convincing evidence to the contrary, claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

17. At page 18, bridging to page 19 of the response received 25 February 2005, hereinafter the response, argument is presented that the office has interpreted the claims as encompassing an embodiment not explicitly supported by the disclosure.

18. The above argument is met with general agreement for the claims are given their broadest reasonable interpretation, and is then balanced against the level of disclosure found. As

presented above, the specification does not provide an adequate written description of conducting the assay in a chip, yet the claimed method encompasses just such an embodiment. In view of the apparent agreement in the lack of an adequate written description, the rejection is maintained.

19. At page 18 of the response argument is presented that the claimed method overcomes the issue of alkaline and alkaline-earth salts, and that the Office has not presented reasoning or art to suggest how the claimed method does not eliminate the salts.

20. The above argument has been fully considered and has not been found persuasive for the claimed method does not recite any step where alkaline salts have been removed from the sample prior to processing. It is noted with particularity that there are a plurality of wells, a channel ad connecting means. The claims and disclosure do not identify just what surface is being washed and what non-bound components are being removed, and to where they are being removed to. For example, is one well being washed whilst the sample is in another, or is the channel being washed, and the wash fluid are being moved to a second well? As a result of the method not specifying where the components are moved to, or more particularly, what they are being separated from, the claims have been interpreted and encompassing an embodiment where the alkaline salts are still present. A review of the figure does not show means for introducing any wash fluid, or its separation from the sample. Furthermore, the figure does not reflect that ere is any mechanism that can serve as a pump that would be used to drive the fluid from one well to that of another.

21. At page 19 of the response argument is presented that "moving a liquid through a channel is a fundamental technique which applicants maintain would be well known to those of ordinary

skill in the art." Argument is also presented at page 19, bridging to page 20 of the response that one could use a syringe to cause pressure such that the fluid flows out of a well and through a channel. At page 20 attention is directed to page 48 of the disclosure.

22. For convenience, the relevant portions of page 48 are reproduced below.

> This application discloses a 96-well plate that can be used for sequencing fragment generation with biotinylated terminators as shown in Figure 12. In the example shown, each end of a channel is connected to a single well. However, for other applications, the end of a channel could be connected to a plurality of wells. Pressure is applied to drive the samples through a glass capillary into the channels on the chip. Inside the channels the biotin is captured by the covalently bound streptavidin. After passing through the channel, the sample enters into a clean plate in the other end of the chip. Pressure applied in reverse drives the sample through the channel multiple times and ensures a highly efficient solid phase capture. Water is similarly added to

As can be seen above, the means for processing the fluid would have each end of a channel in a single well, or the end of a channel could be connected to a plurality of wells. While pressure is to drive the fluid out of the well, through the channel, and into one or more wells, no means other than a perpetual motion could cause this feat to occur. The aspect of using a syringe is not suggested by the disclosure at page 48 or in the figures. Rather, the text at page 48 closely parallels Figure 12 (reproduced above).

23. Rather than directing attention to where support for such pumping means is found in the original disclosure, be it in text or in an associated figure, conclusory argument has been presented as to what one of skill in the art would have known. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

Attention is also directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

Accordingly, and in the absence of convincing evidence to the contrary, the above argument has not been found persuasive towards the withdrawal of the rejection.

24. At page 20, bridging to page 21, of the response argument is presented that the disclosure fairly supports passing of the fluid multiple times through the channel; directing attention to page 48, *supra*.

25. The above argument has not been found persuasive towards the withdrawal of the rejection for while the claims may fairly encompass such an embodiment, the claims only require but a single passage of the sample through the channel. Applicant is reminded that while a claim is to be read as broadly as is reasonably possible, limitations found within the disclosure are not to be read into the claims. In the instant case, the claims have been amended so to recite just such a limitation. The specification, however, provides no more support for generating a reversible force out of thin air than it did for unidirectional force.

26. At page 22 of the response argument is presented that the rejection should at least be modified in that the claims have been amended so to recite MALDI-TOF mass spectrometry, and arguing further that:

> In response to this, applicants note that the claimed method is directed to sequencing a DNA and that the DNA (template) is contacted with the appropriate components for fragment generation.

While applicant's representative has seized upon the use of the indefinite article "a," the claim is not limited to the analysis of fragments generated form only 1 DNA or from only one template. Rather, the claims fairly encompass the analysis of any number of fragments generated from any number of templates, not to mention the random and spurious fragments generated as a result of performing MALDI-TOF, which is recognized in the art as presenting sequencing difficulties/erroneous results, *supra*.

27. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

28. Claims 74-92 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

29. As presented above, the specification has not been found to provide an adequate written description of the invention to where the specification does not reasonably suggest that applicant did not possess the entire invention at the time of filing. It is well settled that one cannot enable that which they do not yet possess.

30. Further, the records clearly shows that the claimed method fairly encompasses embodiments where art-recognized issues of enablement would be encountered, yet the specification is effectively silent as to how they are to be overcome sans the skilled artisan resort to undue experimentation.

31. Therefore, and in the absence of convincing evidence to the contrary, claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to arguments

32. At pages 22-23 of the response applicant's representative asserts that the rejection of claims under 35 USC 112, (enablement) first paragraph, should be withdrawn as a traversal of the rejection of the claims as they relate to failing to satisfy the written description requirement has been made.

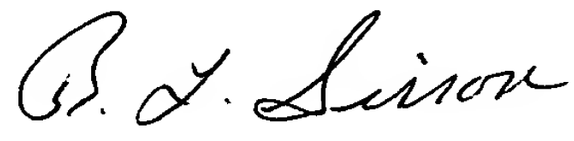
33. As presented above, the rejection of claims as failing to satisfy the written description requirement of 35 USC 112, first paragraph, has been maintained. For the above reasons and in the absence of convincing evidence as to how the specification fully enables the entire scope of the claimed invention, the rejection is maintained.

Conclusion

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

35. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

36. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
13 June 2005